C2

12. (Amended) The method of claim 7, wherein administration is by intravenous infusion.

C3

19. (Amended) The method of claim 17, wherein said method comprises administering docetaxel in at least one dose of 100 mg/m^2.

REMARKS

By this Amendment, claims 6, 10, and 11 are cancelled and claims 7, 12, and 19 are amended. Claim 7 is amended by incorporation of the subject matter of claim 11. Support for the amendment to claim 7 comes from the specification, as originally filed, at page 3, lines 1-4, and original claim 11. Claim 12 is amended solely to maintain proper dependency. Claim 19 is amended to eliminate redundant claim language. Accordingly, no new matter is added by this Amendment. Currently, claims 7-9 and 12-22 are pending in this application, claims 13-15 having been withdrawn by the Examiner as directed to a non-elected invention.

I. *Restriction Requirement*

The Office makes the Restriction Requirement FINAL. (Office Action at page 2.) Applicants respectfully submit that dependent claims 13-15 are encompassed by independent claim 7. Thus, these dependent claims are directed to the same invention as claim 7. Applicants respectfully request that the Office reconsider and withdraw the Restriction Requirement in view of this fact. Alternatively, if the Office does not find this

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argument convincing, Applicants respectfully request that the Office hold the Restriction Requirement in abeyance until allowable subject matter is identified, and then consider rejoinder of the dependent claims with the allowable subject matter.

II. *Rejections Under 35 U.S.C. § 102 and § 103*

A. Placke *et al.* (U.S. Patent No. 6,419,900)

The Office rejects claim 6 under 35 U.S.C. § 102(b) or, in the alternative, under 35 U.S.C. § 103(a) over Placke *et al.* (Office Action at page 3.) By this Amendment, claim 6 is cancelled, rendering the rejection moot. Accordingly, Applicants respectfully request that the Office withdraw this rejection.

B. Broder *et al.* (U.S. Patent No. 6,245,805)

The Office rejects claims 7-12 and 15-22 under 35 U.S.C. § 103(a) over Broder *et al.* (Office Action at page 3.) As the Office recognizes, Broder *et al.* does not disclose a method of treating hepatocellular carcinoma by intravenously administering docetaxel. However, the Office asserts that such a method would be obvious because Broder *et al.* discloses that docetaxel can be parenterally and orally administered, and that oral administration can be used to treat hepatocellular carcinoma. Applicants respectfully traverse this rejection.

In order for the Office to set forth a proper *prima facie* case of obviousness, various factual and legal requirements must be met. One of the requirements is that there must be some teaching, motivation, or suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the cited art to achieve the presently claimed invention. *In re Fine*, 837 F.2d

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1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Another requirement is that a person of ordinary skill in the art must have had a reasonable expectation of success in achieving the presently claimed invention if the cited art were to have been modified as suggested by the Office. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The teaching or suggestion to make the modification, and the reasonable expectation of success must be found in the prior art, and can not be gleaned from the disclosure of Applicant. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP § 2142. Applicants respectfully submit that Broder *et al.* does not provide a motivation to achieve a method of intravenously treating hepatocellular carcinoma with docetaxel. Furthermore, Broder *et al.* does not provide a reasonable expectation of success in achieving such a method.

Broder *et al.* is directed to improving the oral bioavailability of pharmaceutical agents that are poorly absorbed in the gastrointestinal tract. See Broder *et al.* at col. 1, lines 21-25, for example. In one passage of the patent, Broder *et al.* discloses that docetaxel can be co-administered with a multi-drug resistance (MDR) inhibitor to achieve a treatment for hepatocellular carcinoma. See Broder *et al.* at col. 15, lines 32-44. The only data provided relating to treating with docetaxel are given in Figures 30 and 31, and the accompanying text at col. 8, lines 11-24. These portions of Broder *et al.* disclose experiments to monitor the levels of docetaxel in the blood system of rats treated with docetaxel and docetaxel with cyclosporin by intravenous and oral routes. Significantly, Broder *et al.* does not disclose or suggest that such intravenous and oral administration of docetaxel can be used to treat hepatocellular carcinoma. Indeed, there is no disclosure whatsoever of levels of docetaxel in the liver, much less a

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disclosure of any activity of docetaxel, administered intravenously or orally, on hepatocellular carcinoma. Rather, the intravenous administration of docetaxel is performed solely to provide a benchmark (*i.e.*, a positive control) for the presence of docetaxel in the blood system. Oral administration is performed solely to determine if the docetaxel can be absorbed into the blood system.

Broder *et al.* provides no data to show that docetaxel can be used to treat a hepatocellular carcinoma, much less treat a hepatocellular carcinoma by intravenous administration of docetaxel. Rather, what Broder *et al.* shows is that oral co-administration of docetaxel and an MDR inhibitor increases the amount of docetaxel in the blood system as compared to oral administration of docetaxel alone, increasing it almost to the level obtainable by intravenous administration. Thus, the sole disclosure in Broder *et al.* that even remotely relates to a method of treating hepatocellular carcinoma with docetaxel comes from a brief passing comment at col. 15, lines 40-44.

Applicants respectfully submit that, even assuming for the sake of argument that one of ordinary skill in the art could find a motivation to treat a hepatocellular carcinoma with docetaxel based on the general comment at col. 15, lines 40-44, at the most, that person would find a motivation to orally treat the carcinoma. There would be no motivation whatsoever to treat, or even attempt to treat, a hepatocellular carcinoma by intravenous administration of docetaxel, alone or with another agent. Thus, at most, the sole motivation possibly provided by Broder *et al.* is a motivation to achieve a composition and a method of treating that enhances absorption of poorly absorbed drugs that are orally administered. It provides no motivation to achieve any method of administration that is not orally based. Accordingly, it does not, and cannot, provide a

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motivation to achieve the presently claimed invention. For this reason alone, the Office has failed to set forth a *prima facie* case of obviousness over Broder *et al.*

Furthermore, even if one could ignore the fact that Broder *et al.* fails to motivate one of skill in the art to achieve the presently claimed invention, the Office has still failed to set forth a *prima facie* case of obviousness because Broder *et al.* fails to provide a reasonable expectation of success in achieving the presently claimed invention. For example, although Broder *et al.* mentions generally in passing that docetaxel, when orally co-administered with another agent, can be used to treat hepatocellular carcinoma, Broder *et al.* does not provide one of ordinary skill in the art a reasonable expectation of successfully treating hepatocellular carcinoma by intravenously administering docetaxel.

The only data presented by Broder *et al.* that could be considered relevant to treatment of hepatocellular carcinoma is data showing that paclitaxel can be found in the liver after it is administered to a subject. However, this does not show that the paclitaxel is present in an amount sufficient to treat hepatocellular carcinoma (*i.e.*, in an effective amount). Furthermore, it does not show that an effective amount of paclitaxel can be localized to the liver. Finally, and most importantly, this data does not show, or even suggest, that docetaxel can be administered to a patient in an amount sufficient to treat hepatocellular carcinoma.

Finally, with regard to the rejection of dependent claims 17-19 and 22, the Office implies that there would be a reasonable expectation that the same amounts of docetaxel administered orally would be effective intravenously. However, the Office does not provide a reference or any scientific reasoning to support this contention.

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Applicants respectfully submit that one of ordinary skill in the art would immediately recognize that the doses required for oral administration of a drug to achieve an effective level are significantly higher than the doses required for intravenous administration. See, for example, Benet *et al.*, *Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, and Elimination,* In *The Pharmacological Basis of Therapeutics*, 8th Ed., Gilman *et al.* Eds., Pergamon Press, 1990, Chapter 1, page 7 in particular (attached hereto as part of an Information Disclosure Statement). Thus, even if one were motivated to attempt to optimize the methods of Broder *et al.*, that person would pick a relatively high dosage, which would be effective for oral dosing, not a relatively low dosage, which would be effective for intravenous dosing, such as the amounts recited in present claims 17-19 and 22. Thus, Applicants respectfully submit that it would not be obvious to select the amounts of docetaxel recited in claims 17-19 and 22. Accordingly, claims 17-19 and 22 would not be obvious over Broder *et al.*

Because Broder *et al.* neither motivates one of ordinary skill in the art to achieve the presently claimed invention nor provides one of ordinary skill in the art a reasonable expectation of successfully achieving it, Applicants respectfully submit that the Office has failed to set forth a *prima facie* case of obviousness. Therefore, Applicants respectfully request that the Office reconsider and withdraw the rejection of the present claims as obvious over Broder *et al.*

III. *Conclusion*

Applicants respectfully submit that this application is in condition for allowance. Therefore, Applicants respectfully request that the Office reconsider and withdraw the

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outstanding rejections, rejoin claims 13-15 with claims 7-9 and 12-22, and permit this application to issue as a U.S. patent in due course. If the Office believes anything further is necessary in order to place this application in even better condition for allowance, Applicants respectfully request that their undersigned representative be contacted at the telephone number or e-mail address listed below.

Please grant any extensions of time required to enter this Amendment, and charge any required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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Dated: October 15, 2002

By: _____

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Attachment:
Appendix

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APPENDIX

(Accompanying Amendment dated October 15, 2002)

10/083,565

Please amend claims 7, 12, and 19 as follows:

7. (Amended) A method of treating hepatocellular carcinoma, said method comprising administering to a patient docetaxel in an amount sufficient to treat said hepatocellular carcinoma, wherein said administering is intravenous.

12. (Amended) The method of claim [11] 7, wherein administration is by intravenous infusion.

19. (Amended) The method of claim 17, wherein said method comprises administering docetaxel [or a hydrate of docetaxel] in at least one dose of 100 mg/m^2.

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